Kawasaki disease (4), a systemic vasculitis associated with an antigen-driven IgA response (5). Interestingly, increased intestinal permeability has been reported in this disease, suggesting that disrupted intestinal barrier function plays a role in the development of IgA vasculitis (6). Furthermore, chilblain-like lesions with possible vascular damage have been reported to be possibly linked to COVID-19 infection, with anti–COVID-19 serologic testing revealing IgA but no IgG in several patients (7).

Even if we cannot prove the causality of COVID-19, it is notable that in this patient, IgA vasculitis was associated with elevated levels of serum IgA and with only IgA shown on COVID-19 serologic testing. Endothelial injury during COVID-19 infection has recently been reported, with a recent study suggesting that SARS–CoV-2 infection participates in the induction of endotheliitis in several organs as a direct consequence of viral involvement and the host inflammatory response (8).

Dr. Allez has received consulting fees, speaking fees, and/or honoraria from Amgen, Biogen, Boehringer Ingelheim, Celgene, Ferring, Genentech, Janssen, Pfizer, Takeda, Tillotts, and Roche (less than $10,000 each) and research support from Janssen and Genentech. Dr. Battistella has received consulting fees, speaking fees, and/or honoraria from Bristol Myers Squibb, Innate Pharma, and Kyowa Kirin (less than $10,000 each) and research support from Takeda. Dr. Molina has received consulting fees and/or honoraria from Gilead, Merck, ViiV, and Sanofi (less than $10,000 each) and research support from Gilead. No other disclosures relevant to this letter were reported.

Matthieu Allez, MD, PhD
Blandine Denis, MD, PhD
Jean-David Bouaziz, MD, PhD
Maxime Battistella, MD, PhD
Anne-Marie Zagdanski, MD
Jules Bayart, MD
Ingrid Lazaridou, MD
Caroline Gatey, MD
Evangeline Pillebout, MD
Marie-Laure Chaix Baudier, MD
Constance Delaugerre, MD, PhD
Jean-Michel Molina, MD, PhD
Jérôme Le Goff, MD, PhD
Hôpital Saint-Louis, AP-HP and Université de Paris
Paris, France

1. Audemard-Verger A, Pillebout E, Guillevin L, Thervet E, Terrier B. IgA vasculitis (Henoch-Shönlein purpura) in adults: diagnostic and therapeutic aspects [review]. Autoimmun Rev 2015;14:579–85.
2. Marques I, Lagos A, Reis J, Pinto A, Neves B. Reversible Henoch-Schönlein purpura complicating adalimumab therapy. J Crohns Colitis 2012;6:796–9.
3. Padoan A, Sciacovelli L, Basso D, Negrini D, Zuin S, Cosma C, et al. IgA-Ab response to spike glycoprotein of SARS-CoV-2 in patients with COVID-19: a longitudinal study. Clin Chim Acta 2020; 507:164–6.
4. Viner RM, Whittaker E. Kawasaki-like disease: emerging complication during the COVID-19 pandemic. Lancet 2020;395:1741–3.
5. Rowley AH, Shulman ST, Garcia FL, Guzman-Cottrill JA, Miura M, Lee HL, et al. Cloning the arterial IgA antibody response during acute Kawasaki disease. J Immunol 2005;175:8386–91.
6. Noval Rivas M, Wakita D, Franklin MK, Carvalho TT, Abolhesn A, Gomez AC, et al. Intestinal permeability and IgA provoke immune vasculitis linked to cardiovascular inflammation. Immunity 2019;51:508–21.
7. El Hachem M, Diociaiuti A, Concato C, Carsetti R, Carnevale C, Ciofi Degli Atti M, et al. A clinical, histopathological and laboratory study of 19 consecutive Italian paediatric patients with chilblain-like lesions: lights and shadows on the relationship with COVID-19 infection. J Eur Acad Dermatol Venereol 2020. E-pub ahead of print.
8. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet 2020;395:1417–8.

DOI 10.1002/art.41409

Anticardiolipin IgG autoantibody level is an independent risk factor for COVID-19 severity

To the Editor:

A growing body of evidence indicates that patients with cardiovascular complications are at a higher risk for developing severe manifestations of coronavirus disease 2019 (COVID-19) (1). In addition, the high incidence of thromboembolic events suggests that COVID-19–induced coagulopathy plays an important role in disease severity (2). Antiphospholipid autoantibodies (aPLs), which are essential markers of antiphospholipid syndrome, are also considered to be cardiovascular risk factors. The presence of aPLs has recently been described in 3 patients presenting with severe manifestations of COVID-19 (3). Such factors related to the severity of the disease may be relevant in the management of the COVID-19 pandemic, particularly as they pertain to the decision as to whether to keep a newly infected patient in the hospital.

To this end, levels of IgG and IgM anticardiolipin antibodies (aCLs) and anti–β_2-glycoprotein I (anti-β_2GPI) autoantibodies were measured using real-time polymerase chain reaction in serum samples from 56 COVID-19 patients with severe acute respiratory syndrome coronavirus 2 (SARS–CoV-2). The cohort was divided into a moderate (n = 27) and a severe group of patients (n = 29) according to clinical presentation at sampling. A disease manifestation was defined as severe if at least one of the following criteria was met: respiratory rate >30 breaths/minute, oxygen saturation ≤93%, Pa_{O_2}/Fi_{O_2} ratio ≤300 mm Hg, or cardiogenic shock or respiratory failure requiring admission to an intensive care unit (4). All samples were obtained from a declared biobank (DC 2020-4028) in compliance with ethics directives. Enzyme-linked immunosorbent assay kits were used to determine aCL and anti-β_2GPI antibodies. The association between disease severity and the clinical and biologic features of the disease was analyzed by univariate and multivariate logistic regression analyses (generalized linear model function; R software version 4.0).

A summary of our results is provided in Table 1. Additional information regarding materials, methods, and aPL levels are available online (Supplementary Materials and Methods,

Table 1. Association between clinical and biologic features and disease severity analyzed in 56 COVID-19 patients using univariate and multivariate logistic regression analyses*

	Moderate disease	Severe disease†	Univariate OR (95% CI) (*P*)	Multivariate OR (95% CI) (*P*)
Age, mean ± SD years	66.7 ± 19.9	66.6 ± 15.8	1.00 (0.97–1.03) (0.986)	–
Sex				
Female	13 (56.5)	10 (43.5)	Referent	Referent
Male	14 (42.4)	19 (57.6)	1.76 (0.61–5.28) (0.301)	2.56 (0.67–10.40) (0.174)
Duration of symptoms, mean ± SD days	11.5 ± 5.8	14.5 ± 7.1	1.08 (0.99–1.19) (0.094)	1.04 (0.94–1.17) (0.439)
Real-time PCR cycle threshold at diagnosis, mean ± SD	27.9 ± 4.2	27.5 ± 5.2	0.98 (0.88–1.10) (0.764)	–
IgG aCL				
<15 units/ml	24 (60.0)	16 (40.0)	Referent	Referent
≥15 units/ml	3 (18.8)	13 (81.2)	6.50 (1.76–31.77) (0.009)	8.71 (1.76–73.91) (0.017)
IgM aCL				
<15 units/ml	24 (45.3)	29 (54.7)	Referent	–
≥15 units/ml	3 (100.0)	0	0.00 (NA–13×10^{71}) (0.990)	–
Anti-β_2GPI IgG				
<8 units/ml	26 (47.3)	29 (52.7)	Referent	–
≥8 units/ml	1 (100.0)	0	0.00 (NA–95.10^{121}) (0.991)	–
Anti-β_2GPI IgM				
<8 units/ml	25 (48.1)	27 (51.9)	Referent	–
≥8 units/ml	2 (50.0)	2 (50.0)	0.93 (0.10–8.19) (0.941)	–
History of thrombosis				
No	22 (46.8)	25 (53.2)	Referent	–
Yes	5 (55.6)	4 (44.4)	0.70 (0.16–2.98) (0.631)	–
History of stroke				
No	27 (50.0)	27 (50.0)	Referent	–
Yes	0	2 (100.0)	15.10^6 (0.00–NA) (0.992)	–
Coronary heart disease				
No	24 (46.2)	28 (53.8)	Referent	Referent
Yes	3 (75.0)	1 (25.0)	0.29 (0.01–2.40) (0.292)	0.23 (0.01–3.45) (0.316)
High blood pressure				
No	12 (42.9)	16 (57.1)	Referent	Referent
Yes	15 (53.6)	13 (46.4)	0.65 (0.22–1.86) (0.423)	0.89 (0.23–3.41) (0.868)
Heart failure				
No	26 (49.1)	27 (50.9)	Referent	–
Yes	1 (33.3)	2 (66.7)	1.93 (0.17–42.93) (0.602)	–
Diabetes				
No	20 (43.5)	26 (56.5)	Referent	Referent
Yes	7 (70.0)	3 (30.0)	0.33 (0.06–1.35) (0.140)	0.21 (0.02–1.85) (0.175)
Chronic respiratory disease				
No	23 (46.0)	27 (54.0)	Referent	Referent
Yes	4 (66.7)	2 (33.3)	0.43 (0.06–2.39) (0.349)	0.80 (0.08–6.49) (0.835)

* Variables with a *P* value of <0.5 in univariate analysis were used for the multivariate analysis. Association is expressed as the odds ratio (OR) with 95% confidence interval (95% CI). *P* values less than 0.05 were considered significant. Except where indicated otherwise, values are the number (%). PCR = polymerase chain reaction; aCL = anticardiolipin antibodies; NA = not applicable; anti-β_2GPI = anti–β_2-glycoprotein I.

† Coronavirus disease 2019 (COVID-19) manifestation was defined as severe based on whether at least one of the following criteria was met: respiratory rate >30 breaths/minute, oxygen saturation ≤93%, Pao_2/Fio_2 ratio ≤300 mm Hg, or cardiogenic shock or respiratory failure requiring admission to an intensive care unit.

Supplementary Table 1, and Supplementary Figure 1, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41409/abstract). No differences in terms of age, sex, duration of symptoms, history of thrombosis, history of stroke, cardiovascular complications, diabetes, and chronic respiratory disease were observed between the 2 groups of patients. Differences in the aPL profile between the 2 groups were observed only for IgG aCL antibodies. Univariate analyses showed that the levels of IgG aCL were significantly associated with severe COVID-19 manifestations (odds ratio [OR] = 6.50; *P* = 0.009) with further confirmation by multivariate analysis (OR = 8.71; *P* = 0.017). These findings show, for the first time, that IgG aCL antibody levels are highly and independently associated with disease severity. Except for 1 patient who presented with a history of stroke, no other IgG aCL–positive patient with a severe manifestation of COVID-19 presented with a history of thrombosis, which suggests that positivity for aCL could be attributed to infection with SARS–CoV-2. Indeed, viral infections are known to induce aPL, especially aCL that may increase the risk of thrombosis and clot formation in the presence of another thrombophilic condition (5).

Since patients with COVID-19 develop profound hypercoagulation (6), IgG aCL–positive patients are at a higher risk for developing thrombosis, and therefore further follow-up with clinical evaluations and biologic testing is recommended. Recent autopsy data on subjects who died of COVID-19 showed that ~50% of venous thromboembolic events were not recognized prior to death (2), suggesting that some patients may need anticoagulation therapy. While awaiting further investigation, aCL detection could serve as a simple strategy to help stratify COVID-19 patients according to disease severity and thereby help the therapeutic decision-making process.

Daniel Bertin, PharmD, MSc
AP-HM, Hôpital de la Conception
Aix-Marseille Université
and CNRS UMR 7051
Alexandre Brodovitch, PhD
Abdou Beziane, PhD
Sylvia Hug, MD
Afaf Bouamri, PharmD
AP-HM, Hôpital de la Conception
Jean Louis Mege, MD, PhD
AP-HM, Hôpital de la Conception
IRD
and Méditerranée Infection
Xavier Heim, PharmD, MSc
Nathalie Bardin, PharmD, PhD
AP-HM, Hôpital de la Conception
Aix Marseille Université
Center for CardioVascular and Nutrition Research
and INSERM UMRS 1263
Marseille, France

1. Li B, Yang J, Zhao F, Zhi L, Wang X, Liu L, et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China [review]. Clin Res Cardiol 2020;109:531–8.
2. Wichmann D, Sperhake JP, Lütgehetmann M, Steurer S, Edler C, Heinemann A, et al. Autopsy findings and venous thromboembolism in patients with COVID-19. Ann Intern Med 2020;173:268–77.
3. Zhang Y, Xiao M, Zhang S, Xia P, Cao W, Jiang W, et al. Coagulopathy and antiphospholipid antibodies in patients with Covid-19. N Engl J Med 2020;382:e38.
4. Pan A, Liu L, Wang C, Guo H, Hao X, Wang Q, et al. Association of public health interventions with the epidemiology of the COVID-19 outbreak in Wuhan, China. JAMA 2020;323:1915–23.
5. Wang D, Lv W, Zhang S, Zhang J. Advances in the research on anticardiolipin antibody [review]. J Immunol Res 2019;2019:8380214.
6. Bowles L, Platton S, Yartey N, Dave M, Lee K, Hart DP, et al. Lupus anticoagulant and abnormal coagulation tests in patients with Covid-19. N Engl J Med 2020;383:288–90.

DOI 10.1002/art.41434

Frequency and results of cryoglobulin retesting in 4,963 patients: comment on the article by Kolopp-Sarda et al

To the Editor:

Cryoglobulinemia is a rare pathologic condition that is difficult to diagnose both clinically and in the laboratory. Symptoms vary, and there are many difficulties in cryoglobulin detection, beginning with the necessity of maintaining the sample at 37°C during the preanalytical phase until centrifugation in the laboratory. To improve analytical accuracy, some authors have suggested retesting patients, especially when there is strong clinical suspicion, to prevent false-negative results (1). We read with great interest the article by Kolopp-Sarda et al (2), in which they reported that nearly 9% of retested patients who initially tested negative for cryoglobulins received a positive result at follow-up. These results were obtained from a very large collection of samples from 13,439 patients.

We conducted a retrospective study of all cryoglobulin analyses performed over a 5-year period (2015–2019) at our institution. There were 6,716 samples collected from 4,963 patients (mean ± SD age 59 ± 18 years [60% female, 40% male]). Four hundred fifty-five patients whose initial test result for cryoglobulins was negative (11%) were subsequently retested. In 44 of these 455 patients (10%), the initial finding was not confirmed, which supports estimates by Kolopp-Sarda et al. However, Kolopp-Sarda and colleagues did not provide data regarding retesting of patients who initially showed positive results. In our opinion, this approach to retesting is not sufficient, as clinical recommendations suggest that a positive result must be confirmed by a second test after an interval of ≥12 weeks for the classification of cryoglobulinemic vasculitis (3,4). In our study, of the 354 patients who initially tested positive for cryoglobulins, positivity was not confirmed in 17%, independent of the time between initial testing and retesting.

Although results from a single serum sample should not be considered sufficient for making or excluding a diagnosis of cryoglobulinemia, we report poor adherence to recommendations for retesting. In Kolopp-Sarda et al's report, only 18.5% of patients who initially tested negative for cryoglobulins were retested; in our study we documented retesting for only 809 (16%) of all tested patients (11% of patients who initially tested negative and 39% of patients who initially tested positive for cryoglobulins) ($P < 0.001$) (Figure 1), suggesting that clinicians do not order retesting, especially if results are initially negative for cryoglobulins. Our findings indicate that in up to 13% of patients (n = 105), initially reported outcomes are not confirmed on retesting. Our results